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Edema as a Very Early Marker for Acute Myocardial Ischemia

A Cardiovascular Magnetic Resonance Study

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Objectives This study was designed to determine whether imaging myocardial edema would identify acute myocardial ischemia before irreversible injury takes place.

Background Early identification of acute myocardial ischemia is a diagnostic challenge.

Methods We studied 15 dogs with serial T_2-weighted and cine imaging at baseline, during transient coronary occlusion of up to 35 min, and after reperfusion in a 1.5-T magnetic resonance imaging system. Late gadolinium enhancement and troponin measurements were used to assess for the presence of irreversible injury. Myocardial water content was measured to assess myocardial edema.

Results We consistently observed a transmural area of high T_2 signal intensity matching areas with new onset regional akinesia 28 ± 4 min after experimental coronary artery occlusion. At this time, the contrast-to-noise ratio between the ischemic and remote myocardium had significantly increased from 1.0 ± 2.0 to 12.8 ± 9.6 ($p < 0.003$), which further increased after reperfusion to 15.8 ± 10.3 ($p < 0.004$ compared with baseline). Neither myocardial late gadolinium enhancement nor troponin elevation were noted at this time window. Myocardial water content of the ischemic segments was consistently higher (68.9 ± 2% vs. 67.0 ± 2%; $p < 0.004$) than in remote segments and the difference correlated significantly to the contrast-to-noise ratio in T_2 images ($p < 0.04$).

Conclusions We provide the first evidence that T_2-weighted cardiovascular magnetic resonance imaging of edema detects acute ischemic myocyte injury before the onset of irreversible injury. T_2-weighted cardiovascular magnetic resonance imaging may serve as a very useful diagnostic marker in clinical settings such as unstable angina or evolving infarction. (J Am Coll Cardiol 2009;53:1194–201) © 2009 by the American College of Cardiology Foundation

The ultimate goal of any infarct reperfusion strategy is to salvage as much of the area at risk subtended by the infarct-related artery as possible. Time is crucial in this setting because if not timely reperfused, a wave front of irreversible injury gradually replaces the area at risk (1). Therefore, one would ideally seek to identify an evolving acute myocardial infarction (MI) at a very early stage before the onset of irreversible injury. Serum markers of acute myocardial injury, the current clinical gold standard, cannot meet this demand because their detection marks the liberation of myocardial proteins or enzymes from irreversibly damaged myocytes. A more promising strategy could theoretically exploit 1 or more of the phenomena occurring during the ischemic cascade after coronary occlusion, and before actual necrosis ensues. Defective perfusion and loss of regional function appear attractive, yet they are limited by their nonspecificity to *acute* coronary syndromes, as they also are a feature of chronic coronary artery disease. Myocardial edema represents a promising target in this cascade because it precedes myocardial necrosis and can be accurately detected using T_2-weighted cardiovascular magnetic resonance (CMR) (2). Recently, it has been shown that, in the setting of acute reperfused infarction, high signal intensity areas in T_2-weighted images accurately visualize the myocardial area at risk (3,4). This further supports the premise that T_2

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signal abnormality may be an early feature of acute coronary syndromes. Based upon these considerations, we hypothesized that imaging myocardial edema would identify acute myocardial ischemia before irreversible injury takes place.

Methods

Surgical Preparation

Fifteen mongrel dogs (weight 15 to 25 kg) were studied in accordance with the Position of the American Heart Association on Research Animal Use and local ethics committee approval. Anesthesia was induced with 30-mg/kg sodium thiopental. Animals were then intubated and intravenous lines were established. The dogs were then transported to the CMR laboratory. Anesthesia was maintained using 4-mg/h fentanyl citrate and 25-mg/h midazolam. Animals were respirated using Harvard constant volume ventilation with an O_2 and NO_2 gas mixture. The chest wall was opened with left lateral thoracotomy, where the left anterior descending artery was dissected and a snare was placed around the vessel below the first diagonal artery. Lidocaine was administered before occlusion (3 doses, 1 mg/kg, 5 min apart, and then a constant drip 1 mg/min). At the end of the experiment, animals were euthanized with saturated KCl and the heart excised.

Occlusion data were available for 11 dogs, and reperfusion data for 9 (7 with transient and 2 with prolonged ischemia).

CMR Image Acquisition

All images were acquired using a state-of-the-art 1.5-T magnetic resonance imaging system (Avanto, Siemens Medical Solutions, Erlangen, Germany). We used standard electrocardiogram leads and a flexible 8-channel phased-array surface coil, which was secured around the thorax. Localization was performed using breath-hold single-phase steady-state free precession (SSFP) images of true anatomical axes of the heart. All sequences (T_2, SSFP, and late enhancement) were acquired with a slice thickness of 10 mm with no gap in identical slice positions.

Baseline. Retrospectively gated SSFP images were acquired without phase sharing in short-axis views, covering the left ventricle as well as long-axis views (2-, 3-, and 4-chamber, effective repetition time: 40 ms, echo time: 1.1 ms, 25 phases). With a short time-to-inversion recovery sequence including blood flow and fat suppression pulses as previously described (5), breath-hold triple inversion recovery fast spin echo T_2-weighted images were then acquired covering the left ventricle in the same slice locations and planes as the SSFP images (repetition time: 2 R-R intervals, echo time: 61 ms, field of view: 34 to 38 cm, matrix: 256 × 256, echo train length: 15, acquisition window: 150 ms, inversion time: "fat": 170 ms). For T_2-weighted imaging, we acquired images using either surface (dogs #1 to #7) or body (dogs #8 to #15) coil. If surface coil was used, a signal intensity algorithm was applied to correct for the inhomogeneous reception of the phased array coil. In short, a pre-scan normalization filter acquired a low resolution, large field of view scan before data acquisition, which was then smoothed to remove spikes originating from occasional non-Gaussian nature of the image noise. Data were then weighted using the coil characteristic/pre-scan information to remove inhomogeneities from the surface coil.

Abbreviations and Acronyms

CMR = cardiovascular magnetic resonance
CNR = contrast-to-noise ratio
ESWT = end-systolic wall thickening
MI = myocardial infarction
SI = signal intensity
SSFP = steady-state free precession

Occlusion. Immediately after left anterior descending artery occlusion, SSFP and T_2-weighted images were acquired. Thereafter, we obtained T_2-weighted images every 4 to 5 min, until a focal high T_2 signal intensity was visually detectable by 2 agreeing observers, and that fulfilled the following criteria:

- Transmural extent
- Regional distribution consistent with a coronary territory
- Present in at least 2 consecutive short-axis slices
- Confirmation in a cross-sectional long-axis view
- Confirmation in a repeat short-axis view

Reperfusion. Once these criteria were met, the coronary artery occlusion was removed and the vessel was reopened. T_2-weighted and SSFP images were repeated, and late enhancement images with an inversion time selected to null signal of normal myocardium were acquired after intravenous injection of gadolinium-diethylenetriamine pentaacetic acid 0.2 mmol/kg body weight (Magnevist, Bayer Healthcare, Toronto, Ontario, Canada).

In 2 dogs we performed prolonged occlusion followed by reperfusion to induce actual MI.

In 9 dogs, immediately after euthanasia, the heart was divided into 4 to 6 slices of 1-cm thickness each. Each of these slices was further divided into samples of 1 to 2 cm^3, composed of tissue from ischemic and remote myocardium.

Assessment for myocardial water content. Each sample was weighed initially (wet weight), and after drying to a constant weight (72 h) in a desiccating oven. The percent myocardial water content was calculated as: (wet weight − dry weight) × 100 / wet weight.

Troponin measurements. Intravenous samples were obtained at baseline, at the end of occlusion, and finally immediately after reperfusion.

Image Analysis

We used validated software for the evaluation (MASS 6, Medis, Leiden, the Netherlands).

Global and regional function. Endocardial and epicardial contours were manually drawn in diastole and systole for every short-axis slice, and the following parameters were calculated: end-diastolic volume, end-systolic volume, ejection fraction, and myocardial mass.

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Table 1 Changes of LV Volume and Global and Regional Function During the Protocol

	Baseline	Ischemia	Reperfusion	p Value
LV volume				
EDV, ml	70 ± 13	83 ± 17	73 ± 11	0.004
ESV, ml	42 ± 9	67 ± 14	52 ± 9	0.018
Global LV function				
EF, %	39 ± 5	22 ± 5	23 ± 5	0.001
End-systolic wall thickening, %				
Remote segments	47 ± 25	44 ± 25	49 ± 39	0.467
Ischemic segments	43 ± 27	−17 ± 15	15 ± 48	0.0001

The p values are in comparison to baseline.
EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular.

In the slice exhibiting maximal extent of wall motion abnormality, the myocardium was equally divided into 100 radial chords starting from the anterior insertion of the right ventricle, and the percent end-systolic wall thickening (ESWT) was calculated.

T_2-weighted images. The same slice location as selected for calculation of % ESWT was used for quantitative analysis of T_2 signal intensity. Extreme care was taken to avoid including any artificially high signal intensity (SI) due to inadequately suppressed slow flow within the ventricular cavity space (5). The contrast-to-noise ratio (CNR) ($[SI_{ischemic} - SI_{remote}]/SD_{noise}$) between ischemic and remote myocardium was calculated. Ischemic myocardium was defined as myocardial areas with normal baseline % ESWT and loss of wall thickening early after occlusion, and inferior myocardium retaining its ESWT after occlusion was considered remote. Regions of interests were drawn within areas of maximal T_2 SI in the newly developed akinetic zone, as well as in remote myocardium and background noise.

Statistics

All statistical tests were performed using a commercially available statistical program (SPSS 16 for Macintosh, SPSS Inc., Chicago, Illinois). Data are presented as mean ± SD. We tested for data normalcy using the Kolmogorov-Smirnov test. Continuous variables were compared using the paired Student *t* test. Repeated measurements general linear model was used to compare the baseline, occlusion,

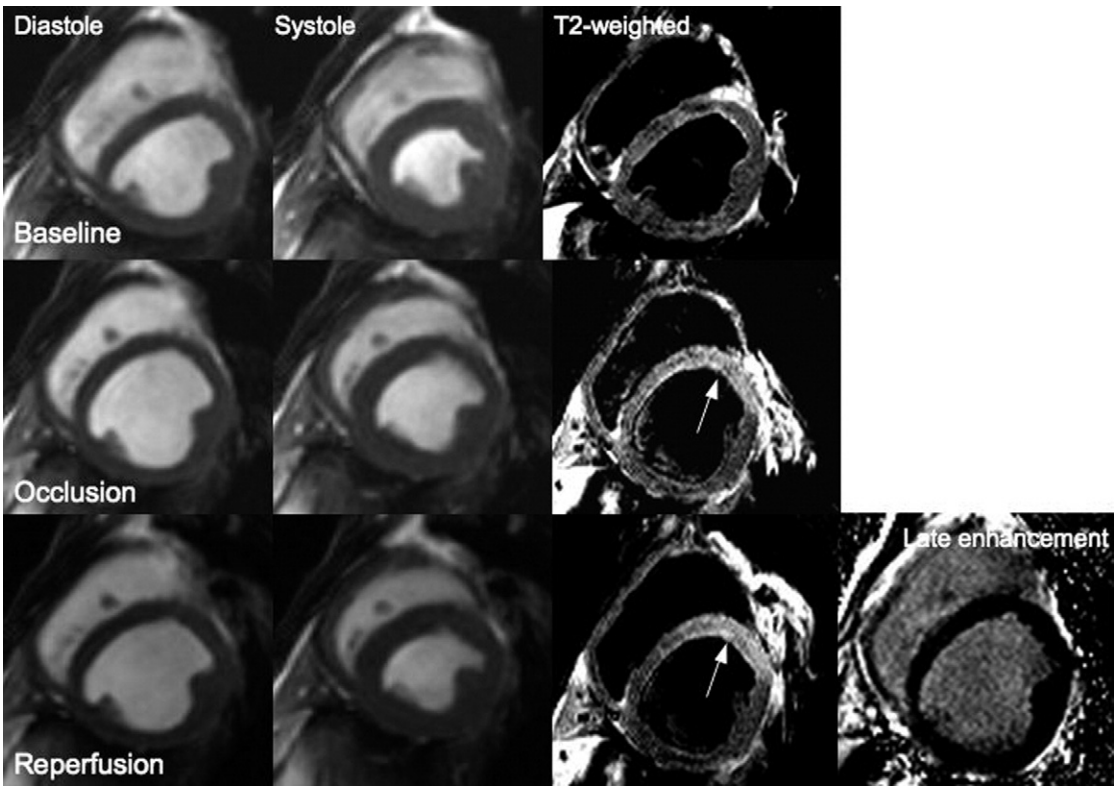

Figure 1 CMR Findings on Function, T_2-Weighted, and Late Enhancement: Images in Dog #4 Undergoing Reperfusion After Visual Detection of High T_2 SI

Baseline: Lack of regional wall motion abnormalities, homogenous T_2 signal pattern. Occlusion: Cardiovascular magnetic resonance (CMR) images 26 min after onset of coronary occlusion with transmural high T_2 signal of the anterior myocardium **(arrow)**, matching a regional wall motion abnormality. Reperfusion: CMR data 5 min after reperfusion with mildly improved wall motion but markedly increased T_2 signal **(arrow)**. No evidence for irreversible injury (lack of late enhancement). Accompanying Videos (1.1, 1.2, and 1.3) of left ventricular function at baseline, after occlusion, and at reperfusion are available online. SI = signal intensity.

and reperfusion data. Data were correlated using the Spearman correlation coefficient. A value of $p < 0.05$ was considered significant.

Results

In 1 dog (#3), the study had to be interrupted after onset of ischemia due to technical problems. Three dogs died immediately before (#13) and after (#2 and #9) occlusion, and 2 dogs (#6 and #15) died after reperfusion (all due to therapy-resistant ventricular fibrillation). Thus, occlusion data was available for 11 dogs and reperfusion data for 9 (7 with transient and 2 with prolonged ischemia).

Global and regional left ventricular function. Table 1 shows the mean changes in volume, function, and signal intensity during the experimental protocol. Compared with baseline, there was an increase of end-diastolic and end-systolic volumes, with a reduced ejection fraction during occlusion. Regional function, as defined by ESWT, declined dramatically immediately after occlusion. Upon reperfusion, we observed improvement of global and regional function.

T_2-weighted images. Immediately after coronary occlusion, despite the presence of a significant regional loss of contractility within 20 min, there was no consistent change in SI in any dog. However, thereafter all animals showed a segmental, transmural area of high T_2 SI, matching the distribution of the observed wall motion abnormality (Figs. 1 and 2). The change in SI was visually apparent at a mean of 28 ± 4 min (range 21 to 34 min) after the onset of coronary occlusion. At this time, the CNR between the ischemic and remote myocardium had significantly increased from 1.0 ± 2.0 to 12.8 ± 9.6 ($p < 0.003$), which further increased after reperfusion to 15.8 ± 10.3 ($p = 0.37$ compared with occlusion and 0.004 compared with baseline, intergroup differences: $p < 0.001$) (Fig. 3). The baseline, occlusion, and reperfusion CNR values in the 2 dogs with MI were: dog #1: 4.0, 15.5, and 46.5 and dog #8: 1.2, 5.7, and 15.8, respectively. Figure 4 demonstrates the findings in 1 dog (#1) without early (i.e., immediately after visual identification) reperfusion. The area of SI change, as observed 34 min after onset of ischemia, accurately matched the area of

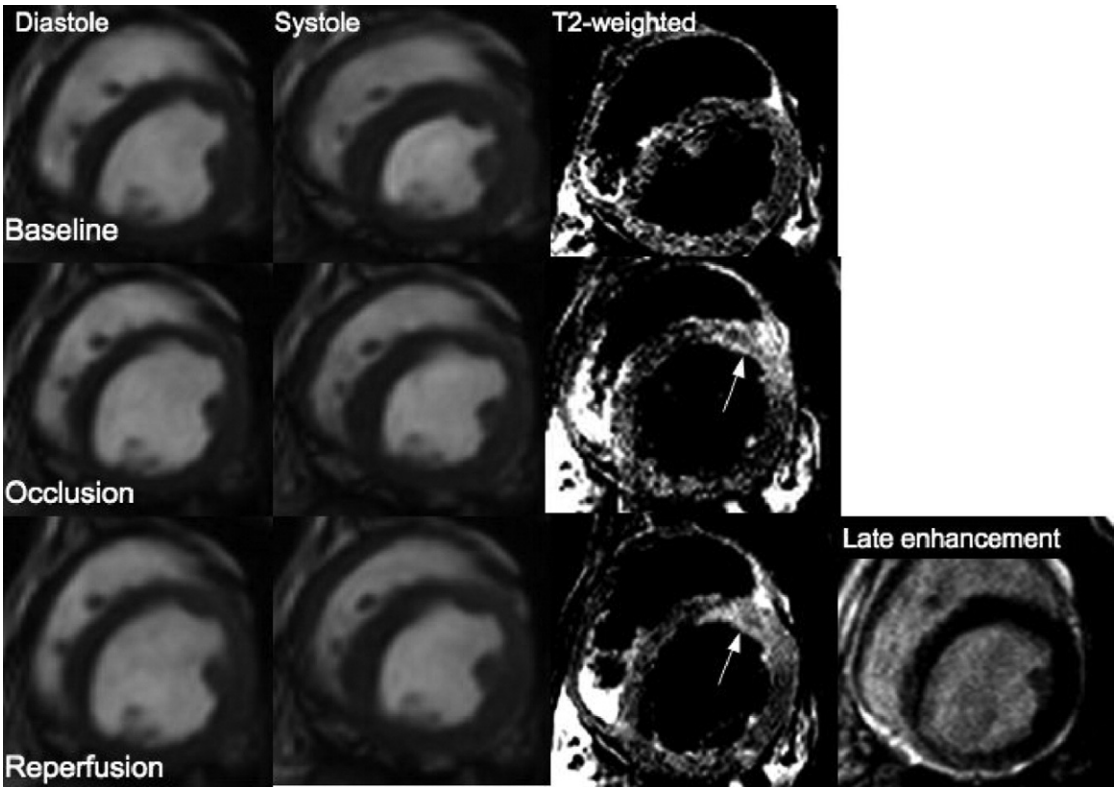

Figure 2 **CMR Findings on Function, T_2-Weighted, and Late Enhancement: Images in Dog #7 Undergoing Reperfusion After Visual Detection of High T_2 SI**

Baseline: Lack of regional wall motion abnormalities, homogenous T_2 signal pattern. Occlusion: CMR images 31 min after onset of coronary occlusion with transmural high T_2 signal of the anterior myocardium **(arrow)**, matching a regional wall motion abnormality. Reperfusion: CMR data 5 min after reperfusion with mildly improved wall motion but markedly increased T_2 signal **(arrow)**. No evidence for irreversible injury (lack of late enhancement). Accompanying Videos (2.1, 2.2, and 2.3) of left ventricular function at baseline, after occlusion, and at reperfusion are available online. Abbreviations as in Figure 1.

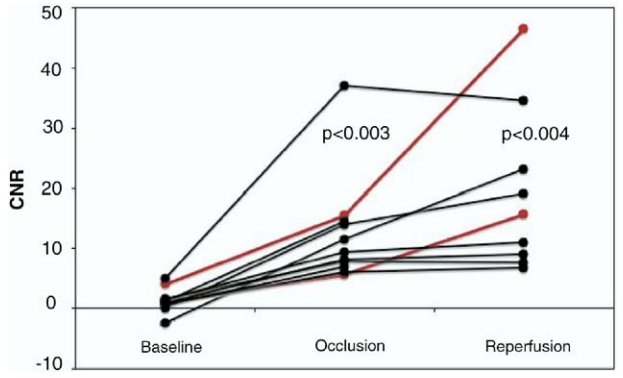

Figure 3 **CNR of Ischemic to Remote Myocardium in T_2-Weighted Images at Baseline, After Occlusion, and After Reperfusion**

Data from the 2 dogs (#1 and #8) who underwent prolonged occlusion are highlighted in **red**. Note that the occlusion data from these 2 dogs are not end occlusion data; they demonstrate the contrast-to-noise ratio (CNR) at the earliest time point at which a high T_2 signal was visually detectable.

irreversible injury defined by late enhancement after 90 min of occlusion and subsequent reperfusion.

Myocardial water content. Data were available from 8 animals: 7 noninfarcted (dogs #5, #6, #7, #10, #11, #12, and #14) as well as from 1 infarcted dog (#8). Water content of the ischemic segments was consistently greater (68.9 ± 2% vs. 67.0 ± 2%; $p < 0.004$) than that of remote segments in every dog (absolute difference: 1.8 ± 0.9%). The difference was 9% in the dog (#8) who underwent prolonged occlusion to induce MI. There was a significant correlation between the difference in myocardial water content difference (ischemic minus remote segments) and post-reperfusion T_2-weighted CNR values ($r = 0.77$; $p = 0.04$).

Troponin measurements. Data were available from 7 animals: 6 noninfarcted (dogs #4, #5, #7, #10, #12, and #14) as well as from 1 infarcted dog (#8). Troponin values remained in the normal range (baseline: 0.09 ± 0.02 ng/ml, end-occlusion: 0.10 ± 0.04 ng/ml, immediate post-reperfusion: 0.13 ± 0.04 ng/ml; p = NS) throughout the experiment. In the dog undergoing MI (#8), troponin was in the normal range at baseline and during occlusion but was only slightly elevated immediately after reperfusion (0.36 ng/ml, normal limit <0.2 ng/ml).

Discussion

To the best of our knowledge, this is the first report introducing myocardial edema imaging as a novel early marker of acute myocardial ischemia before the onset of irreversible injury. Recent reports in animal models (4) and humans (6) after acute MI confirmed that T_2 signal abnormalities are consistently larger than the area of irreversible injury (late gadolinium enhancement). We hypothesized that this discrepancy in spatial distribution may reflect the difference in the temporal evolution of both myocardial edema (T_2-weighted) and necrosis (late gadolinium enhancement). Specifically if one could trace this relation back in time, then it is likely that at a certain point, one would encounter myocardial edema in the absence of any irreversible injury, which was the snapshot we sought to capture in this experiment.

Our study shows that transient myocardial ischemia leads to a visually apparent signal intensity increase in T_2-weighted CMR images, before the onset of late gadolinium enhancement reflecting irreversible myocyte injury. This adds to previous reports of T_2-related SI changes in MI (7,8). In contrast to previous studies, our data relate to transient episodes likely leading to reversible myocyte injury, rather than myocyte destruction. Thus, our data can be used to address questions in the clinical settings of very early infarct stages or brief episodes of transient ischemia preceding MI (9).

During the ischemic cascade following coronary artery occlusion, function deteriorates very early due to its high adenosine triphosphate demand (10). Immediately thereafter, myocytes swell due to failure of energy-regulated membrane channels, with subsequent sodium and water influx (11,12). If ischemia persists, cell membranes disintegrate marking the onset of actual necrosis. These facts explain our findings: the "still intact" myocyte membrane early after coronary occlusion did not allow either troponin release into the blood stream nor regional gadolinium-diethylenetriamine pentaacetic acid accumulation, both of which were negative in our series.

A strong body of evidence supports our findings that T_2-weighted signal intensity changes reflect regional myocardial edema because of the long T_2 relaxation time of protons bound in free water (3,13–15). In a dog model of acute MI, Higgins et al. (2) demonstrated that an increase in myocardial water content of 1% to 3%, which is similar to that we observed, is associated with considerable T_2 prolongation in ischemic myocardium.

Clinical implications. Although our study has validated the concept of early ischemia detection using edema imaging, the clinical application of this premise in various scenarios could only be realized after carefully addressing several logistical and safety issues related to patient transport, monitoring, and setup. If these issues can be addressed appropriately, T_2-weighted CMR imaging could offer a noninvasive, noncontrast approach applicable to patients with acute chest pain but nondiagnostic electrocardiography and "still" normal serum markers, possibly allowing for very early detection of myocardial ischemia. This is of particular relevance, as the resulting delay of appropriate therapeutic interventions is linked to a poorer outcome for patients (16–18). This approach would also allow for the detection of very recent episodes of ischemia, such as intermittent angina, that often precede MI (9), using the T_2 signal as a tissue "memory function." Furthermore, in patients with suspected ischemia and a history of previous infarcts, T_2-weighted imaging could reliably differentiate acute ischemia from chronic infarcts (19). T_2-weighted imaging could also

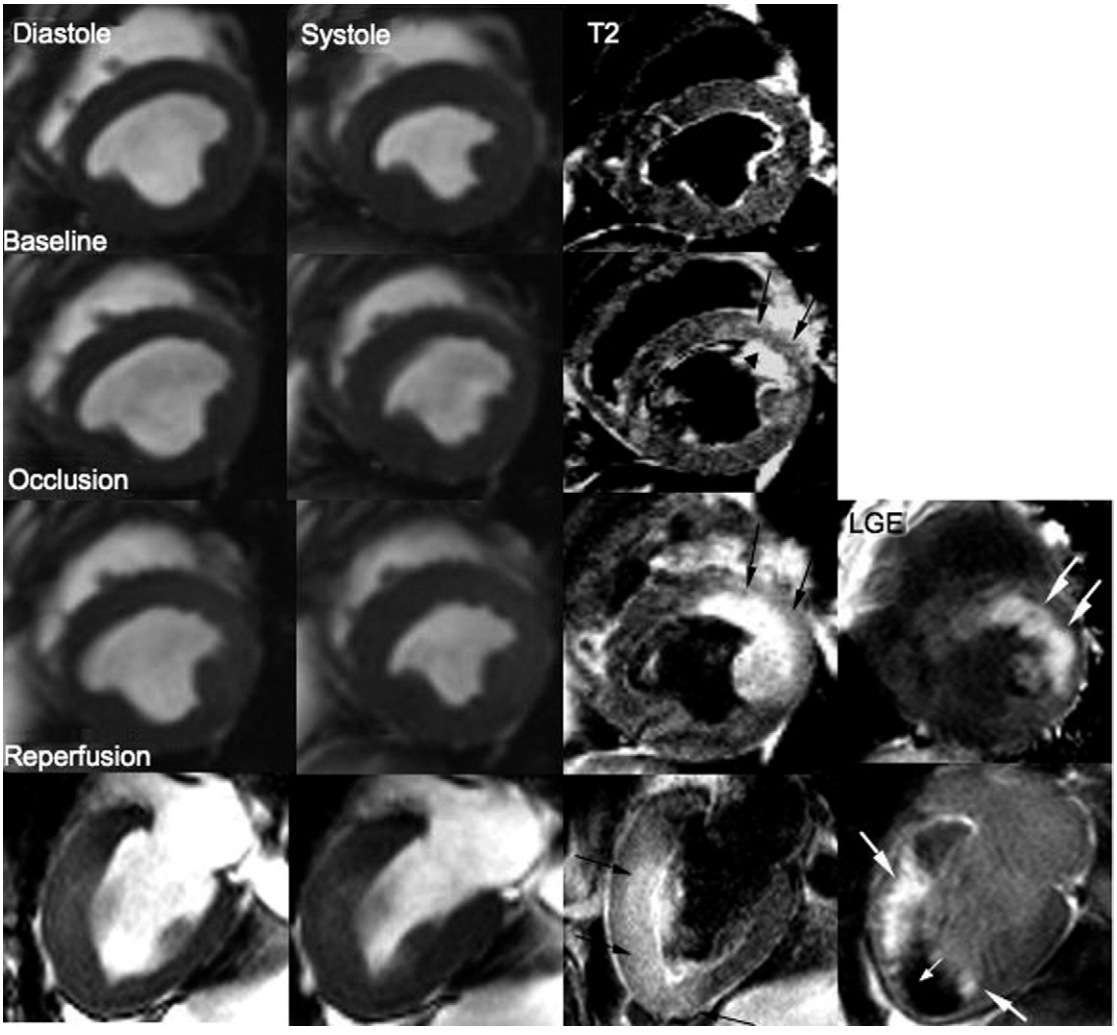

Figure 4 **CMR Findings on Function, T_2-Weighted, and Late Enhancement: Images in Dog #1 With Reperfusion After 90 Min of Ischemia**

Baseline: Lack of regional wall motion abnormalities, homogenous T_2 signal pattern. Occlusion: CMR images obtained 34 min after onset of ischemia with transmurally increased T_2 signal **(arrows)** of the anterior myocardium, matching a regional wall motion abnormality. Note the inadequate blood suppression adjacent to the akinetic anterior wall with high intraluminal T_2 signal **(arrowhead)**, which should not be confused with the developing myocardial high T_2 signal. Reperfusion: CMR images after 90-min occlusion and 5 min of reperfusion: left ventricular function (short- and long-axis views), T_2-weighted, and late enhancement images. The anterior myocardium is now extensively swollen and the transmural high T_2 signal intensity is more pronounced. Late enhancement images indicate extensive irreversible injury **(white arrows)** and microvascular obstruction **(small white arrow)**. Accompanying Videos (4.1, 4.2, and 4.3) of left ventricular function at baseline, after occlusion, and at reperfusion are available online. LGE = late gadolinium enhancement; other abbreviations as in Figure 1.

provide the ideal tool to monitor patients with early revascularized infarcts, in an "aborted infarction" concept (20). The "footprint" of myocardial ischemia in the area at risk may also aid in differentiating aborted infarction, from clinically similar conditions (masquerading infarction), where reperfusion therapy may be contraindicated (20). Finally, the salvaged area at risk may serve as a novel, very strong end point for clinical trials investigating the success of reperfusion strategies.

Limitations and technical considerations. We studied a model of acute total occlusion in healthy animals with induced single-vessel occlusion and without pre-existing coronary artery disease. At this point, the degree to which these data can be extrapolated to clinical situations other than acute total occlusion remains uncertain. Accordingly, the application of T_2-weighted CMR in each such situation will need to be investigated further in relevant clinical settings. Evaluation of emergency room patients presenting with chest pain of initially uncertain origin is certainly desirable. Conversely, patients with acute total occlusions and ischemia similar to the extent of that produced in this study are typically identified without delay. In view of the importance of achieving immediate revascularization in acute ST-segment elevation MI, even a brief delay for a

CMR study may seem difficult to justify. This may however be different in patients with inferolateral infarction, which may remain undetected by electrocardiography.

We used late enhancement instead of triphenyltetrazolium chloride staining to identify irreversible myocardial injury. Preparation of even some heart slices for triphenyltetrazolium chloride staining would not have allowed for myocardial water content measurement in the entire ischemic bed. Because differences in water content are small in this setting, we opted to maximize the sensitivity of detecting water content changes by including the entire ischemic region for analysis. Furthermore, given that late enhancement imaging of necrosis is very accurate and that it can detect even very small infarcts (21), the possibility of missing an infarct in our study is highly unlikely. Finally, the time course of our experiments (30-min occlusion) is generally not associated with irreversible injury in canine hearts (22). The availability of long-term full-functional recovery data would have provided relevant clinical perspective. Yet, we wanted to relate the myocardial water content to CMR findings, which required that animals had to be immediately euthanized after the CMR examination for water content assessment. The troponin results may not reflect the presence of infarction, as they were acquired immediately after occlusion and after reperfusion. However, our aim was to illustrate that at the time window within which T_2 signal changes were readily visible, troponin measurements would not have been able to detect any ischemic injury. Although the increase in CNR between baseline and occlusion was systematic in all animals, the magnitude of this change showed considerable variation between canines (Fig. 3). Likewise, the variability of response to vessel reopening could perhaps be relevant for future studies of reperfusion injury.

The third inversion pulse used for fat suppression in the sequence we implemented could perhaps have introduced a T_1 effect. This may be particularly pronounced at elevated heart rates and may also result from the 2 R-R interval triggers in the spin echo sequence used. However, this approach has probably maximized the contrast between edematous and normal myocardium. Only tissues with long T_1 and long T_2 exhibit increased signal resulting in a "water image," as these relaxation properties are known to be characteristic of water only. Through-motion-related signal loss in the posterolateral segments is occasionally observed in turbo spin echo T_2 imaging, which may lead to an artifactual signal gradient between hypokinetic and normokinetic segments. We addressed this possibility by implementing relative (in relation to baseline images) rather than absolute contrast differences. As is shown in the figures, the contrast we observed was due to progressive SI increases in ischemic myocardium, with no change in SI of remote segments. Unsuppressed slow flow in relation to hypokinetic segments results in high SI (5). This was carefully excluded by analyzing the T_2 images side by side with the cine images. Moreover, the elevated T_2 SI that we observed was transmural in all cases.

The use of surface coil correction algorithms removes most, but not all surface coil effects. However, these effects are static and do not vary between baseline, occlusion, and reperfusion, and so they have minimal bearing on our findings. Furthermore, our findings were consistent and independent of the coil type (surface or body).

We did not perform follow-up studies. Thus, the persistence of the T_2-related findings is unknown, and applicability of our results for clinical settings is limited.

Conclusions

We provide the first evidence that T_2-weighted CMR imaging of edema detects acute ischemic myocyte injury before the onset of irreversible injury.

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Key Words: cardiovascular magnetic resonance ■ acute myocardial ischemia ■ myocardial edema ■ myocardial infarction ■ myocardial viability.

APPENDIX

For the accompanying videos of left ventricular function at baseline, after occlusion, and at reperfusion, please see online version of this article.